Chapter 8
Vitamin D

Summary of the role of vitamin D in human metabolic processes

Vitamin D is required to maintain normal blood levels of calcium and phosphate, that are in turn needed for the normal mineralisation of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Vitamin D achieves this after its conversion to the active form 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D], or calcitriol. This active form regulates the transcription of a number of vitamin D–dependent genes coding for calcium-transporting proteins and bone matrix proteins.

Vitamin D also modulates the transcription of cell cycle proteins, that decrease cell proliferation and increase cell differentiation of a number of specialised cells of the body (e.g., osteoclastic precursors, enterocytes, keratinocytes, etc.). This property may explain the actions of vitamin D in bone resorption, intestinal calcium transport, and skin. Vitamin D also possesses immuno-modulatory properties that may alter responses to infections *in vivo*. The cell differentiating and immuno-modulatory properties underlie the reason why vitamin D derivatives are now used successfully in the treatment of psoriasis and other skin disorders.

Clinical assays measure 1,25-$(OH)_2D_2$ and 1,25-$(OH)_2D_3$, collectively called 1,25-$(OH)_2$D. Similarly, calcidiol is measured as 25-OH-D but it is a mixture of 25-OH-D_2 and 25-OH-D_3. For the purposes of this document, 1,25-$(OH)_2$D and 25-OH-D will be used to refer to calcitriol and calcidiol, respectively.

Overview of the role of vitamin D

Vitamin D, a seco-steroid, can either be made in the skin from a cholesterol-like precursor (7-dehydrocholesterol) by exposure to sunlight or can be provided pre-formed in the diet (*1*). The version made in the skin is referred to as vitamin D_3 whereas the dietary form can be vitamin D_3 or a closely related molecule of plant origin known as vitamin D_2 . Because vitamin D can be made in the skin, it should not strictly be called a vitamin, and some nutritional texts refer to the substance as a prohormone and to the two forms as cholecalciferol (D_3) or ergocalciferol (D_2).

From a nutritional perspective, the two forms are metabolised similarly in humans, are equal in potency, and can be considered equivalent. It is now firmly established that vitamin D_3 is metabolised first in the liver to 25-hydroxyvitamin-D (25-OH-D or calcidiol) (*2*) and subsequently in the kidneys to 1,25-$(OH)_2$D (*3*) to produce a biologically active hormone. The 1,25-$(OH)_2$D, like all vitamin D metabolites, is present in the blood complexed to vitamin D binding protein, a specific α-globulin. The 1,25-$(OH)_2$D is believed to act on target cells similarly to the way a steroid hormone would act. Free hormone crosses the plasma membrane and interacts with a specific nuclear receptor known as the vitamin D receptor, a DNA-binding, zinc-finger protein with a molecular weight of 55,000 (*4*). This ligand-receptor complex binds to a specific vitamin D–responsive element and, with associated transcription factors (e.g., retinoid X receptor), enhances transcription of mRNAs which code for calcium-transporting proteins, bone matrix proteins, or cell cycle–regulating proteins (*5*). As a result of these processes ,1,25-$(OH)_2$D stimulates intestinal absorption of calcium and phosphate and mobilises calcium and phosphate by stimulating bone resorption (*6*). These functions serve

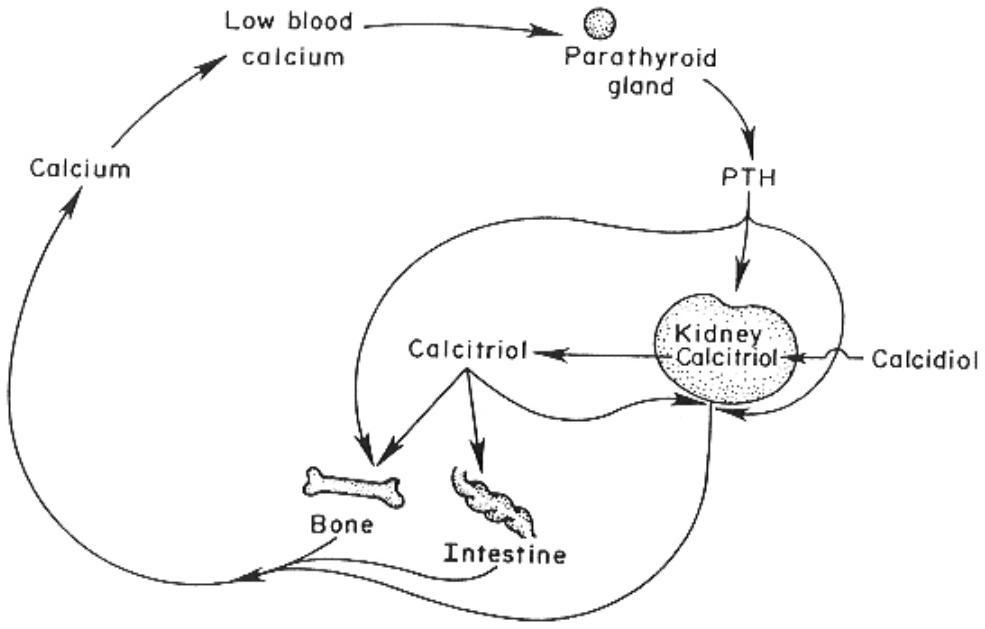
the common purpose of restoring blood levels of calcium and phosphate to normal when concentrations of the two ions are low.

Lately, interest has focused on other cellular actions of 1,25-$(OH)_2$D. With the discovery of 1,25-$(OH)_2$D receptors in many classical non-target tissues such as brain, various bone marrow–derived cells, skin, thymus, etc. (*7*), the view has been expressed that 1,25-$(OH)_2$D induces fusion and differentiation of macrophages (*8, 9*). This effect has been widely interpreted to mean that the natural role of 1,25-$(OH)_2$D is to induce osteoclastogenesis from colony forming units–granulatory monocytes in the bone marrow. The 1,25-$(OH)_2$D also suppresses interleukin 2 production in activated T lymphocytes (*10, 11*), an effect which suggests the hormone might play a role in immuno-modulation *in vivo*. Other tissues (e.g., skin) are directly affected by exogenous administration of vitamin D, though the physiologic significance of these effects is poorly understood. The pharmacologic effects of 1,25-$(OH)_2$D are profound and have resulted in the development of vitamin D analogues, that are approved for use in hyper-proliferative conditions such as psoriasis (*12*).

In calcium homeostasis 1,25-$(OH)_2$D works in conjunction with parathyroid hormone (PTH) to produce its beneficial effects on the plasma levels of ionised calcium and phosphate (*5, 13*). The physiologic loop (***Figure 10***) starts with calcium sensing by the calcium receptor of the parathyroid gland (*14*). When the level of ionised calcium in plasma falls, PTH is secreted by the parathyroid gland and stimulates the tightly regulated renal enzyme 25-OH-D-1-α-hydroxylase to make more 1,25-$(OH)_2$D from the large circulating pool of 25-OH-D. The resulting increase in 1,25-$(OH)_2$D (with the rise in PTH) causes an increase in calcium transport within the intestine, bone, and kidney. All these events raise plasma calcium levels back to normal, that in turn is sensed by the calcium receptor of the parathyroid gland. The further secretion of PTH is turned off not only by the feedback action of calcium, but also by a short feedback loop involving 1,25-$(OH)_2$D directly suppressing PTH synthesis in the parathyroid gland (not shown in figure).

Figure 10

Calcium homeostasis



Source: Adapted from Jones *et al*. (*13*).

Although this model oversimplifies the events involved in calcium homeostasis it is easy to see from it that sufficient 25-OH-D must be available to provide adequate 1,25-$(OH)_2D$ synthesis and hence an adequate level of plasma calcium and that vitamin D deficiency will result in inadequate 25-OH-D and 1,25-$(OH)_2D$ synthesis, inadequate calcium homeostasis, and a constantly elevated PTH level (termed: secondary hyperparathyroidism).

It becomes evident from this method of presentation of the role of vitamin D that the nutritionist can focus on the plasma levels of 25-OH-D and PTH to gain an insight into vitamin D status. Not shown but also important is the endpoint of the physiologic action of vitamin D, namely adequate plasma calcium and phosphate ions, that provide the raw materials for bone mineralisation.

Populations at risk for vitamin D deficiency

Infants

Infants constitute a population at risk for vitamin D deficiency because of relatively large vitamin D needs brought about by their high rate of skeletal growth. At birth, infants have acquired *in utero* the vitamin D stores that must carry them through the first months of life. A recent survey of French neonates revealed that 64 percent had 25-OH-D values below 30 nmol/l, the lower limit of the normal range (*15*). Breast-fed infants are particularly at risk because of the low concentrations of vitamin D in human milk (*16*). This problem is further compounded in some infants fed human milk by a restriction in exposure to ultraviolet (UV) light for seasonal, latitudinal, cultural, or social reasons. Infants born in the autumn months at extremes of latitude are particularly at risk because they spend the first 6 months of their life indoors and therefore have little opportunity to synthesise vitamin D in their skin during this period. Consequently, although vitamin D deficiency is rare in developed countries, sporadic cases of rickets are still being reported in many northern cities but almost always in infants fed human milk (*17-20*).

Infant formulas are supplemented with vitamin D at levels ranging from 40 international units (IUs) or 1 μg /418.4 kJ to 100 IU or 2.5 μg /418.4 kJ, that provide approximately between 6 μg and 15 μg of vitamin D, respectively. These amounts of dietary vitamin D are sufficient to prevent rickets.

Adolescents

Another period of rapid growth of the skeleton occurs at puberty and increases the need not for the vitamin D itself, but for the active form 1,25-$(OH)_2D$. This need results from the increased conversion of 25-OH-D to 1,25-$(OH)_2D$ in adolescents (*21*). Furthermore, unlike infants, adolescents are usually outdoors and therefore usually are exposed to UV light sufficient for synthesising vitamin D for their needs. Excess production of vitamin D in the summer and early fall months is stored mainly in the adipose tissue (*22*) and is available to sustain high growth rates in the winter months that follow. Insufficient vitamin D stores during these periods of increased growth can lead to vitamin D insufficiency (*23*).

Elderly

Over the past 20 years, clinical research studies of the basic biochemical machinery handling vitamin D have suggested an age-related decline in many key steps of vitamin D action (*24*) including rate of skin synthesis, rate of hydroxylation leading to activation to the hormonal form, and response of target tissues (e.g., bone) as well as reduced skin exposure (*25*). Not surprisingly a number of independent studies from around the world have shown that there appears to be vitamin D deficiency in a subset of the elderly population, as characterised by low blood levels of 25-OH-D coupled with elevations of plasma PTH and alkaline

phosphatase (*26*). There is evidence that this vitamin D deficiency contributes to declining bone mass and increases the incidence of hip fractures (*27*). Although some of these studies may exaggerate the extent of the problem by focusing on institutionalised individuals or in-patients with decreased sun exposures, in general they have forced health professionals to re-address the intakes of this segment of society and look at potential solutions to correct the problem. Several groups have found that modest increases in vitamin D intakes (between 10 and 20 µg/day) reduce the rate of bone loss and the fracture rate (*25-29*).

These findings have led agencies and researchers to suggest an increase in recommended vitamin D intakes for the elderly from the suggested 2.5–5 µg /day to a value that is able to maintain normal 25-OH-D levels in the elderly, such as 10–15 µg/day. This vitamin D intake results in lower rates of bone loss and is suggested for the middle-aged (50–70 years) and old-aged (>70 years) populations (*33*). The increased requirements are justified mainly on the grounds of the reduction in skin synthesis of vitamin D, a linear reduction occurring in both men and women, that begins with the thinning of the skin at age 20 years (*24*).

Pregnancy and lactation

Elucidation of the changes in calciotropic hormones occurring during pregnancy and lactation has revealed a role for vitamin D in the former but probably not the latter. Even in pregnancy, the changes in vitamin D metabolism which occur, namely an increase in the maternal plasma levels of 1,25-$(OH)_2$D (*34*) due to a putative placental synthesis of the hormone (*35*), do not seem to impinge greatly on the maternal vitamin D requirements. The concern that modest vitamin D supplementation might be deleterious to the foetus is not justified. Furthermore, because transfer of vitamin D from mother to foetus is important for establishing the newborn's growth rate, the goal of ensuring adequate vitamin D status with conventional prenatal vitamin D supplements probably should not be discouraged.

In lactating women there appears to be no direct role for vitamin D because increased calcium needs are regulated by PTH-related peptide (*36, 37*), and recent studies have failed to show any change in vitamin D metabolites during lactation (*38, 39*). As stated above, the vitamin D content of human milk is low (*16*). Consequently, there is no great drain on maternal vitamin D reserves either to regulate calcium homeostasis or to supply the need of human milk. Because human milk is a poor source of vitamin D, rare cases of nutritional rickets are still found, but these are almost always in breast-fed babies deprived of sunlight exposure (*17-20*). Furthermore, there is little evidence that increasing calcium or vitamin D supplements to lactating mothers results in an increased transfer of calcium or vitamin D in milk (*38*). Thus, the current thinking, based on a clearer understanding of the role of vitamin D in lactation, is that there is little purpose in recommending additional vitamin D for lactating women. The goal for mothers who breast-feed their infants seems to be merely to ensure good nutrition and sunshine exposure in order to ensure normal vitamin D status during the perinatal period.

Table 19

Randomised, controlled trials with dietary vitamin D supplements

Reference	Study Group	n [b]	Age (years) Mean	Age (years) SD	Regimen	Duration (years)	Results[a]
Dawson-Hughes *et al.*, 1991 (*28*)	Healthy, post-menopausal women living independently	249	62	0.5	10 µg vitamin D + 400 mg calcium	1.0	Reduced late wintertime bone loss from vertebrae; net spine BMD; no change in whole-body BMD.
Chapuy *et al.,* 1992 (*29*)	Healthy, elderly women living in nursing homes or in apartments for the elderly	3270	84	6	20 µg vitamin D + 1200 mg calcium	1.5	Hip fractures 43% ; non-vertebral fractures 32%; in subset (*n*=56), BMD of proximal femur 2.7% in vitamin D group and 4.6% in placebo group.
Chapuy *et al.,* 1994 (*30*) [c]						3.0	Hip fractures 29%; non-vertebral fractures 24%.
Dawson-Hughes *et al.,* 1995 (*31*)	Healthy post-menopausal women living independently	261	64	5	2.5 µg or 17.5 µg vitamin D + 500 mg calcium	2.0	Loss of BMD from femoral neck lower in 17.5µg group (-1.06%) than in 2.5 µg group (-2.54%); no difference in BMD at spine.
Lips *et al.,* 1996 (*32*)	Healthy elderly living independently, in nursing homes, or in apartments for the elderly	2578 (1916-Fem.) (662-Male)	80	6	10 µg vitamin D		No difference in fracture incidence; in subset (*n*=248) of women from nursing homes, BMD 2.3% after 2 years.

[a] ↑ Increase; ↓ decrease.
[b] Number of subjects enrolled in the study.
[c] Same study as Chapuy *et al.* (*29*) after further 1.5 years of treatment.
Source: Adapted with permission from Shearer (*25*).

Evidence used for estimating recommended vitamin D intake

Lack of accuracy in estimating dietary intake and skin synthesis

The unique problem of estimating total intake of a substance that can be provided in the diet or made in the skin by exposure to sunlight makes it difficult to estimate adequate total intakes of vitamin D for the general population. Accurate food composition data are not available for vitamin D, accentuating the difficulty for estimating dietary intakes. Whereas this has led two recent US national surveys to avoid attempting this task, the second National Health and Nutrition Examination Survey (NHANES II) estimated vitamin D intakes to be 2.9 µg/day and 2.3 µg/day for younger and older women, respectively. A recent study of elderly women by Kinyamu *et al.* (*40*) concurred with this assessment, finding an intake of 3.53 µ g/day.

Skin synthesis is equally difficult to estimate, being affected by such imponderables as age, season, latitude, time of day, skin exposure, sun screen use, etc. In vitamin D – replete individuals, estimates of skin synthesis are put at around 10 µg /day (*24, 41*), with total intakes estimated at 15 µg/day (*24*).

Use of plasma 25-OH-D as a measure of vitamin D status

Numerous recent studies have used plasma 25-OH-D as a measure of vitamin D status, and there is a strong presumptive relationship of this variable with bone status. Thus, it is not surprising that several nutritional committees (e.g., the Food and Nutrition Board of the US National Academy of Sciences' Institute of Medicine in conjunction with Health Canada) have chosen to use a biochemical basis for estimating required intakes and used these estimates to derive recommended intakes (*33*). The method used involved the estimation of the mean group dietary intake of vitamin D required to maintain the plasma 25-OH-D levels above 27 nmol/l, that is necessary to ensure normal bone health. Previously, many studies had established 27 nmol/l as the lower limit of the normal range (e.g., NHANES III [*41*]). This dietary intake of vitamin D for each population group was rounded to the nearest 50 IU (1.25 µg) and then doubled to cover the needs of all individuals within that group irrespective of sunlight exposure. They termed this amount *adequate intake* (AI) and used it in place of recommended dietary allowance (RDA), that had been used by US agencies since 1941. We are recommending the use of those figures here as recommended nutrient intakes (RNIs) because it is an entirely logical approach to estimating the vitamin D needs for the whole population.

Table 20

Preliminary unweighted results from NHANES III data[a]

Percentile	25-OH-D[b] ng/ml
1st	7.6
5th	10.9
10th	13.2
50th	24.4
90th	40.1
95th	45.9
99th	59.0

[a]Total number of samples used in data analysis: 18,323; mean 25-OH-D value for United States: 25.89 ng/ml (+/- 11.08). Frequency distribution of serum or plasma 25-OH-D. Values for all ages, ethnicity groups, both sexes.[b]High values: four values 90-98 ng/ml, one value of 160.3 ng/ml. Values < 5 ng/ml (lowest standard) entered arbitrarily in the database as "3". Source: NHANES III (*42*).

Because study after study had been recommending increases in vitamin D intakes for the elderly, it might have been expected that the proposed increases in suggested intakes from 5 µg/day (RDAs in the United States [*43*], RNIs in Canada [*44*]) to 10 µg/day or 15 µg/day (AI) would be welcomed. However, a recent editorial in a prominent medical journal attacked the recommendations as being too conservative (*45*). This came on the heels of an article in the same journal (*46*) reporting the level of hypovitaminosis D to be as high as 57 percent in a population of ageing (mean 62 years) medical in-patients in the Boston area.

Of course, such in-patients are by definition sick and should not be used to calculate normal intakes. Indeed, the new NHANES III study (*42)* of 18 323 normal individuals from all regions of the United States suggests that approximately 5 percent had values of 25-OH-D below 27 nmol/l (*47*) (***Table 20***). Although the data are skewed by sampling biases that favour sample collection in the southern states in winter months and northern states in the summer months, even subsets of data collected in northern states in September give the incidence of low 25-OH-D in the elderly in the 6–18 percent range (*47*) as compared with 57 percent in the institutionalized in-patient population (*43*). Ideally, such measurements of the normal population should be made at the end of the winter months and before UV irradiation has reached a strength sufficient to allow skin synthesis of vitamin D. Thus, the NHANES III study may still underestimate the incidence of hypovitaminosis D in a northern elderly population in winter. Nevertheless, in lieu of additional studies of selected human populations, it would seem that the recommendations of the Food and Nutrition Board are reasonable guidelines for vitamin D intakes, at least for the near future. This considered approach allows for a period of time to monitor the potential shortfalls of the new recommendations as well as to assess whether the suggested guidelines can be attained, a point that was repeatedly stated about the RDAs.

Considerations in viewing recommended intakes for vitamin D

In recommending intakes for vitamin D, it must be recognised that in most locations in the world in a broad band around the equator (between latitudes 42°N and 42°S), the most physiologically relevant and efficient way of acquiring vitamin D is to synthesise it endogenously in the skin from 7-dehydrocholesterol by sun (UV) light exposure. In most situations, approximately 30 minutes of skin exposure (without sunscreen) of the arms and face to sunlight can provide all the daily vitamin D needs of the body (*24*). However, skin synthesis of vitamin D is negatively influenced by factors which may reduce the ability of the skin to provide the total needs of the individual (*24*):

- latitude and season – both influence the amount of UV light reaching the skin;
- the ageing process – thinning of the skin reduces the efficiency of this synthetic process;
- skin pigmentation: the presence in the skin of darker pigments interferes with UV light reaching the appropriate layer of the skin;
- clothing – virtually complete covering of the skin for medical, social, cultural, or religious reasons leaves insufficient skin exposed to sunlight; and
- sunscreen use – widespread and liberal use of sun-blockers reduces skin damage by the sun but also deleteriously affects synthesis of vitamin D.

Because not all of these problems can be solved in all geographic locations, particularly during winter at latitudes higher than 42° where synthesis is virtually zero, it is

recommended that individuals not synthesising vitamin D should correct their vitamin D status by consuming the amounts of vitamin D appropriate for their age group (***Table 21***).

Summary of the RNIs for vitamin D by age group

Table 21

RNIs for vitamin D according to age groups

Age group	RNI µg/day
Infants	
0–6 months	5
7–12 months	5
1–3 years	5
4–6 years	5
7–9 years	5
Adolescents, 10–18 years	5
Adults	
19–50 years	5
Older adults, 51–65 years	10
Elderly adults, 65+ years	15
Pregnant women	5
Lactating women	5

[a]Units: for vitamin D, 1 IU = 25 ng, 40 IU = 1 µg, 200 IU = 5 µg, 400 IU = 10 µg, 600 IU = 15 µg, 800 IU = 20 µg; for 25-OH-D, 1 ng/ml = 2.5 nmol/l, 10 ng/ml = 25 nmol/l, 11 ng/ml = 28.5 nmol/l (low limit), 30 ng/ml = 75 nmol/l (normal), 60 ng/ml = 150 nmol/l (upper limit).

Vitamin D toxicity

The adverse effects of high vitamin D intakes – hypercalciuria and hypercalcemia – do not occur at these new recommended intake levels. In fact, it is worth noting that the recommended intakes for all age groups are still well below the lowest observed adverse effect level of 50 µg/day and have not yet even reached the no observed adverse effect level of 20 µg/day (*33, 48*). Outbreaks of idiopathic infantile hypercalcemia in the United Kingdom in the post–World War II era led to the withdrawal of vitamin D fortification from all foods in that country because of concerns that they were due to hypervitaminosis D. There are some suggestions in the literature that these outbreaks of idiopathic infantile hypercalcemia may have been multifactorial with genetic and dietary components and were not just due to technical problems with over-fortification as was assumed (*49,50*). In retrospect, the termination of the vitamin D fortification may have been counter productive because it exposed segments of the UK community to vitamin deficiency and may have discouraged other nations from starting vitamin D fortification programmes (*50*). This is all the more cause for concern because hypovitaminosis D is still a problem worldwide, particularly in developing countries at high latitudes and in countries where skin exposure to sunlight is discouraged (*51*).

Future research

Further research is needed to determine:

- whether vitamin D supplements during pregnancy have any positive effects later in life;
- whether vitamin D has a role in lactation;
- the long-term effects of higher vitamin D intakes;
- whether dietary vitamin D supplements are as good as exposure to UV light; and
- whether vitamin D is only needed for regulation of calcium and phosphate.

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